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Immunity Methods in Scarlet Fever and Measles, by R. A. O'Brien, C.B.E.,
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Scarlet Fever.

WE can fairly say that the basis of a sound means of prevention, diagnosis and treatment of scarlet fever is laid. Much remains to be done, but we know to-day that the patient with typical scarlet fever is positive to the Dick test in the earliest stages, will give a positive Schultz-Charlton blanching response, will yield from throat swab an almost pure culture of hæmolytic streptococci which readily produce Dick toxin, and will become negative to the Dick test during convalescence—further that during the stage of toxæmia, mild or severe, the administration of potent antitoxin will cause a rapid disappearance of symptoms. We know also that we can immunise those who are Dick positive and protect them. This all represents a great advance, but it is important that we should recognise the many gaps in our knowledge and the need for further observation and clinical research. The Dick test is usually but not invariably positive in the patient admitted during the early stage of scarlet fever. (The variations in the statistics dealing with this point in different parts of the world will probably lessen or disappear when there has been international agreement on the strength of Dick toxin to be used for testing.) Whether the suggestion arising out of the very interesting work in America by Dochez (*Journal of Experimental Medicine*, 1927, XLVI., 487) and colleagues, *i.e.*, that the Dick test is a purely allergic response to the protein or other constituent of the streptococcus and is not a response to true toxin as in the Schick test, is true or not, we do not at present know. As opposed to this hypothesis it appears to be reasonably certain that if one allows only nurses who react negatively to the Dick test to take duty in scarlet fever wards, one finds that these nurses do not catch scarlet fever. Further, one can consistently convert the reaction of “ Dick positive ” children, who have been in contact with scarlet fever, to negative in 24 to 48 hours by giving 5 c.c. of concentrated scarlet fever antitoxin. These children remain negative for some days and do not develop scarlet fever. The hypothesis that the reaction is a pure reaction to toxin similar to the Schick response is in accordance with these observations and is the simpler one to hold for the moment while further research is proceeding.

Schultz-Charlton Test.

This test is being used for diagnosis. Its value and its limitations are being more clearly ascertained.

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Active Immunisation.

It is a matter for regret that the important questions of optimum dosage of prophylactic, and interval between injections, have not been more widely investigated in England. When more detailed knowledge is available it will be easier to progress rapidly with "double" or simultaneous immunisation against diphtheria and scarlet fever.

The average patient suffering from moderate uncomplicated scarlet fever will lose his rash and be on the way to recovery by about the fifth to seventh day. At this time the Dick positive percentage amongst patients begins to drop. The immunological phenomena seem clear—the patient will lose his rash promptly if given sufficient antitoxin to make him negative to the Dick test; if untreated with serum he cures himself by the development of antitoxin, at first hidden in his cells, then rapidly produced in abundance and easily detectable in the blood. It is probable that if we could choose a dose of toxin which when given to the average Dick positive reactor would produce an amount of constitutional disturbance, rash, vomiting, temperature, etc., for five days, comparable to that produced by an average attack of scarlet fever, we would achieve a similarly rapid immunity. In-as-much as the dose of toxin is a self-limited one—and not as in true scarlet fever a possibly unlimited quantity produced by the growing streptococci in the throat—the patient would be almost certainly safe from any real harm. One could thus probably immunise against scarlet fever in seven to fourteen days a patient willing to put up with the inconvenience outlined above. It is known as the result of early experiments, some unintentional, some not, that a dose of toxin sufficient to cause "scarlatinoid syndrome" produces rapid immunity. This is, of course, impracticable as a general means of immunisation.

In immunisation with toxin, the tendency is towards large dosage. Dr. W. H. Park, kindly informed me recently that he is giving 30,000 to 40,000 doses in five injections. Amongst 10,000 children in institutions there have been no cases of scarlet fever amongst the immunised children. Of the children strongly positive to the Dick test before immunisation, about 20 per cent. changed to positive within 2 years. I am indebted to the courtesy of Dr. G. L. Keifer, Commissioner, Department of Health, Michigan, for the information that the present practice in that state is to give three doses, two weeks apart, of 500, 3,500 and 30,000 skin doses. This course is yielding a high immunisation rate. On the other hand, it is of interest that Kinloch, Smith and Taylor (*Journal of Hygiene*, 1927, XXVI., 339) with much smaller dosage, *i.e.*, weekly injections of 500, 1,000 and 3,000 skin doses, record a Dick negative percentage of 75, four months later.

Some work has been done with toxin treated with formalin and sodium ricinoleate. We have not been successful in producing a satisfactory for-

malinised toxoid. Professor Perkins (*Journal of the American Medical Association*, 1927, 89, p. 39) records the treatment of 8,000 children with ricinoleated toxoid. When only one dose had been given the incidence per 1,000 was two and one half-times greater in the untreated, and when two doses had been given it was more than six and one-half times. It is possible that equally favourable results have not been obtained elsewhere, or that controlled experiments have not been done in U.S.A., on a sufficiently large scale, for this immunisation with ricinoleate toxoid has not yet come into general use.

Serum Treatment.

The dosage of antitoxin in ordinary attacks of scarlet fever has become more or less standardised and ranges from 10 c.c. intramuscularly in the mild case to 50 or more c.c. in the severe attack, the antitoxin being given intravenously at least in grave cases. Dosage waits to some extent on more accurate methods of titration. Of the methods of titration in which human volunteers are necessary, the determination of the minimum efficient prophylactic dose (*i.e.*, from 2.5 c.c. to 5 c.c. of a good concentrated serum) is probably the most accurate, the Dick skin neutralisation method next and the Schultz-Charlton dilution method last. The Parish-Okell rabbit method is probably at least as accurate as any of the others and has the great advantage that it does not require human volunteers. Serum is efficient in cutting short temperature, malaise and rash, and shortening convalescence, and when given early apparently reduces the chance of the occurrence of complications, but if septic complications such as otitis, mastoiditis or septic adenitis do make their appearance, no serum yet produced seems to promise a certain cure or amelioration. Cases are from time to time reported in which the injection of serum during this septic stage has been followed by rapid improvement; many clinicians will probably therefore feel it their duty to try serum even in septic cases until a more efficient means of treatment is discovered.

Convalescents.

With regard to the formidable question of the discharge of convalescents after scarlet fever without danger to the fellow members of the family and school-fellows, little progress has been made. It is certain that many convalescents are discharged with hæmolytic streptococci present in the throat undistinguishable from true scarlet fever streptococci by any test we possess. Since the streptococci may persist for many months in a considerable number of children, a rigid policy of incarceration of these children until the throat is clear is impracticable. The medical officer of health at present faced with

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this difficult situation can merely adhere to the safe rule that as soon as a convalescent is restored to completely normal health with no discharge from any mucous membrane, etc., he may return to his home, but as long as he has any discharge of any kind he should not be released without grave consideration. A demand for "negative cultures" before release would at present probably quickly clog administrative measures.

An interesting method of trying to abolish "return" cases has been tried by American workers and by Kinloch and colleagues (*loc. cit.*). All contacts are Dick tested and the positive reactors given three or four doses of toxin, e.g., 500, 1,000, 3,000, skin doses at five-day intervals. The latter authors reported that by this method they were able to make a reasonable percentage of contacts negative before the patient returned from hospital.

Measles.

From the laboratory side there is unfortunately but little progress to report. The evidence for and against Caronia's organism, Ruth Tunnicliff's coccus and the virus which Degkwitz hoped to demonstrate in his cultures has changed but little since the survey by McCartney (*Lancet*, 1927, Vol. 1, page 93). His verdict against these three claims was "not proven" or perhaps a little more adverse. Some further clinical work with the serum made from the Tunnicliff coccus, suggesting a content of antitoxin, has been published recently. It is probably fair to say that immunologists generally are at present unconvinced.

A good deal of evidence suggests that the cause is a filterable virus. If we can find a susceptible animal with which we can work we may indulge in the hope that we may have the same success in preparing an efficient vaccine and serum as has been achieved in recent work in connexion with filterable viruses, e.g., Foot and Mouth Disease (Waldmann and the recent English and French work), Dog Distemper (Laidlaw and Dunkin), Yellow Fever (Hindle), Fowlpox (*v.* recent papers by Todd), Avian Roup (Beach, Dalling et al.), etc.

At present, however, our only generally accepted specific method of combating measles is the use of human convalescent serum. Dr. Sutherland and Dr. Anderson have kindly allowed me to quote from a paper to be published shortly, recording complete protection at Monsall in every instance—some 18 in all—where convalescent human serum had been used.

This field is being comprehensively dealt with by Dr. Lethem whose paper I have been privileged to see.

SUMMARY AND CONCLUSIONS.

Scarlet Fever.

The Dick test, Schultz-Charlton test, active immunisation and the use of antitoxin have been firmly established. An anti-serum which will combat septic conditions that have already appeared, is urgently required.

The "convalescent carrier" problem is still unsolved.

Measles.

The utility of convalescent serum for conferring either temporary complete protection or for giving active lasting immunity, dependent on the time of giving, is accepted. The problem for public health authorities is to provide and maintain a supply of serum by appeals for volunteers.
